WORLD CONGRESS ON Gastrointestinal Cancer

ESMO

GEMSTONE-304: A Phase 3 study of sugemalimab plus chemotherapy versus chemotherapy as first-line treatment of patients with unresectable locally advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC)

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Disclosure

- Jing Ni, Chenglin Qu, Bo Wang, Yan Xu, Jin Hu, Qingmei Shi, and Jason Yang are employed by CStone Pharmaceuticals (Suzhou) Co., Ltd.
- All other authors declare no competing interests.
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Introduction

Esophageal squamous cell carcinoma (ESCC) is the most common subtype of esophageal cancer, representing about 84% of all cases worldwide[1]

Programmed death 1 (PD-1) inhibitors plus chemotherapy previously investigated in phase 3 studies of advanced ESCC[2-8], however, limited evidence available for programmed death-ligand 1 (**PD-L1) inhibitor** in the first-line setting

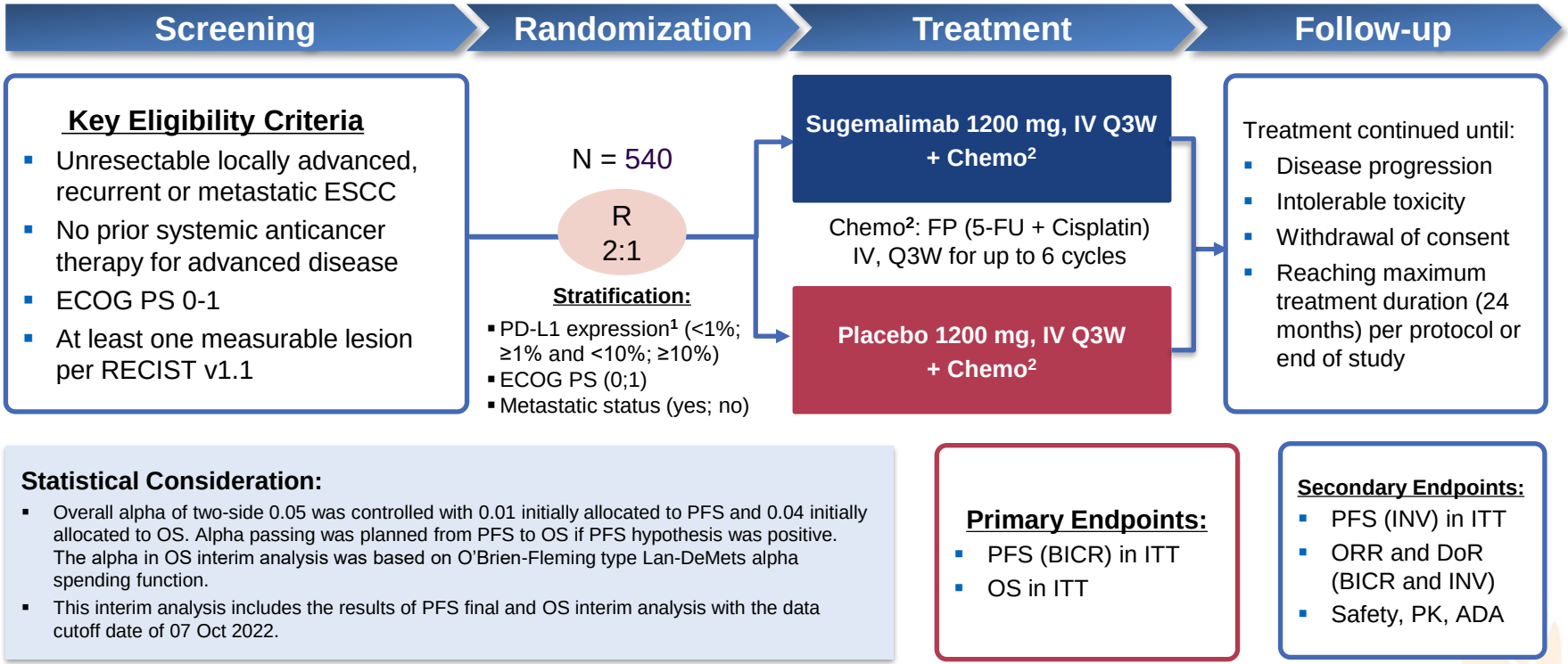
Sugemalimab – a full-length, fully human IgG4 monoclonal **anti-PD-L1** antibody with retained antibody-dependent cellular phagocytosis activity, which differs from other Fc-null anti-PD-L1 antibodies

Prior multicentre phase 1b study demonstrated promising efficacy results and a manageable safety profile of sugemalimab plus 5-fluorouracil and cisplatin in treatment-naïve patients with advanced ESCC[9]

We present the primary analysis from **GEMSTONE-304** trial, a randomized, double-blinded, multicentre, phase 3 study of sugemalimab plus chemotherapy (5-fluorouracil plus cisplatin) versus chemotherapy alone as first-line treatment in patients with advanced ESCC

1. Arnold M et al. *Gut* 2020;69(9):1564-71. 2.Doki Y et al. *N Engl J Med* 2022;386(5):449-62. 3.Lu Z et al. *BMJ* 2022;377:e068714. 4. Luo H et al. *JAMA* 2021;326(10):916-25. 5. Song Y et al. *Nature medicine* 2023;29 (2):473-82. 6. Sun JM et al. *Lancet* 2021;398 (10302):759-71. 7.Wang ZX et al. *Cancer cell* 2022;40(3):277-88.e3. 8. Xu J et al. *The Lancet Oncology* 2023. 9. Shen L *Ann Oncol* 2020;31.

GEMSTONE-304 Study Design (NCT04187352)



Statistical Consideration:

- Overall alpha of two-side 0.05 was controlled with 0.01 initially allocated to PFS and 0.04 initially allocated to OS. Alpha passing was planned from PFS to OS if PFS hypothesis was positive. The alpha in OS interim analysis was based on O'Brien-Fleming type Lan-DeMets alpha spending function.
- This interim analysis includes the results of PFS final and OS interim analysis with the data cutoff date of 07 Oct 2022.

Primary Endpoints:

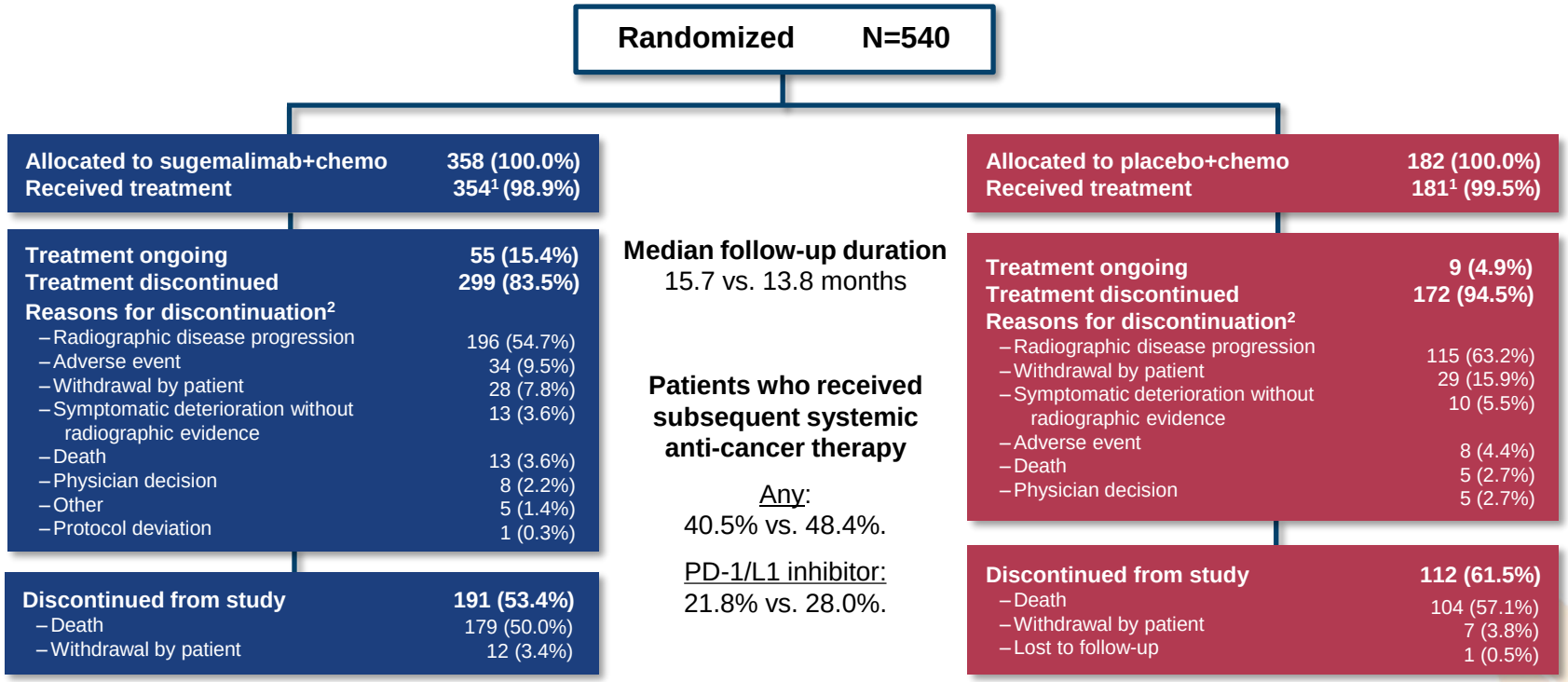
- PFS (BICR) in ITT
- OS in ITT

Secondary Endpoints:

- PFS (INV) in ITT
- ORR and DoR (BICR and INV)
- Safety, PK, ADA

1. PD-L1 expression levels were determined by the percentage of the total number of tumor cells and mononuclear inflammatory cells with positive staining over the number of viable tumor cells. 2. Chemotherapy (cisplatin 80 mg/m^2 on day 1 plus 5-fluorouracil 800 mg/m^2/day on day 1-4) every 3 weeks for up to 6 cycles. ADA: Anti Drug Antibody; BICR:blinded independent central review; DoR: duration of response; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ESCC: Esophageal Squamous Cell Cancer; FP: fluorouracil and cisplatin; INV: investigator; ITT: intent-to-treat; IV:intravenously; ORR: objective response rate; OS: overall survival; PD-L1: programmed death-ligand 1;PFS: progression-free survival; PK: Pharmacokinetics; Q3W: every 3 weeks; R: randomized.

Patient Disposition



Data cutoff date: 07 Oct, 2022.

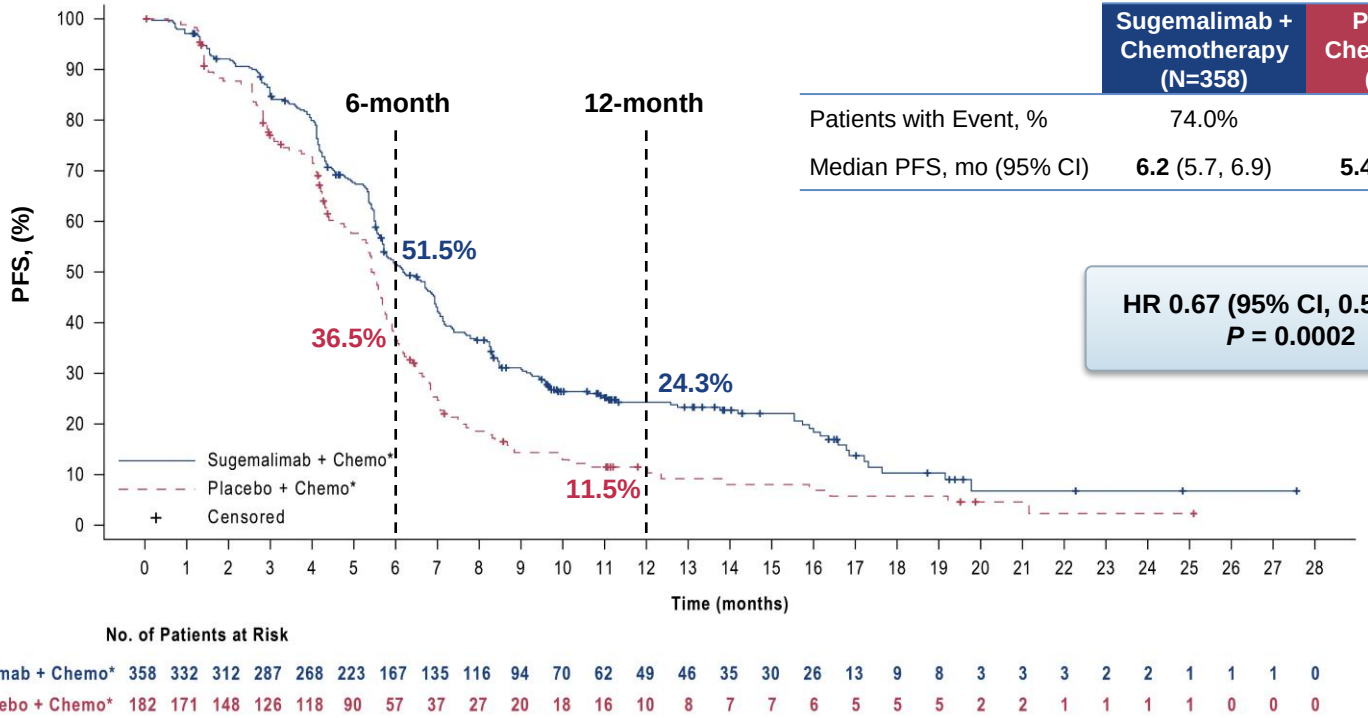
1.There were four and one patient in the two groups, respectively, who were randomized but did not receive any treatment. And one patient assigned to the sugemalimab+chemotherapy group received chemotherapy but not sugemalimab, therefore, this patient was included in the sugemalimab+chemotherapy group for the intent-to-treat set and in the placebo+chemotherapy group for the safety analysis set. 2. Reasons for discontinuation of sugemalimab or placebo. Chemo: chemotherapy

Demographic and Baseline Characteristics

	Sugemalimab + Chemotherapy (N=358)	Placebo + Chemotherapy (N=182)
Age (years), median (range)	62.5 (40, 75)	63.0 (43, 75)
<65	216 (60.3%)	106 (58.2%)
≥65	142 (39.7%)	76 (41.8%)
Sex		
Male	314 (87.7%)	158 (86.8%)
Female	44 (12.3%)	24 (13.2%)
Race		
Asian	358 (100.0%)	182 (100.0%)
Baseline ECOG PS		
0	75 (20.9%)	39 (21.4%)
1	283 (79.1%)	143 (78.6%)
PD-L1 Expression[1]		
<1%	41 (11.5%)	21 (11.5%)
≥1% and <10%	163 (45.5%)	83 (45.6%)
≥10%	154 (43.0%)	78 (42.9%)
Prior Cancer Therapies		
Yes	80 (22.3%)	40 (22.0%)
No	278 (77.7%)	142 (78.0%)
Metastatic	285 (79.6%)	144 (79.1%)
Distant Lymph Node Metastasis	184 (51.4%)	100 (54.9%)
Lung Metastasis	111 (31.0%)	50 (27.5%)
Liver Metastasis	65 (18.2%)	34 (18.7%)
Bone Metastasis	33 (9.2%)	19 (10.4%)

Data cutoff date: 07 Oct, 2022.
1.PD-L1 expression levels were determined by the percentage of the total number of tumor cells and mononuclear inflammatory cells with positive staining over the number of viable tumor cells.
ECOG PS: Eastern Cooperative Oncology Group performance status; PD-L1:programmed death-ligand 1.

Dual Primary Endpoints: BICR-assessed PFS in ITT Population

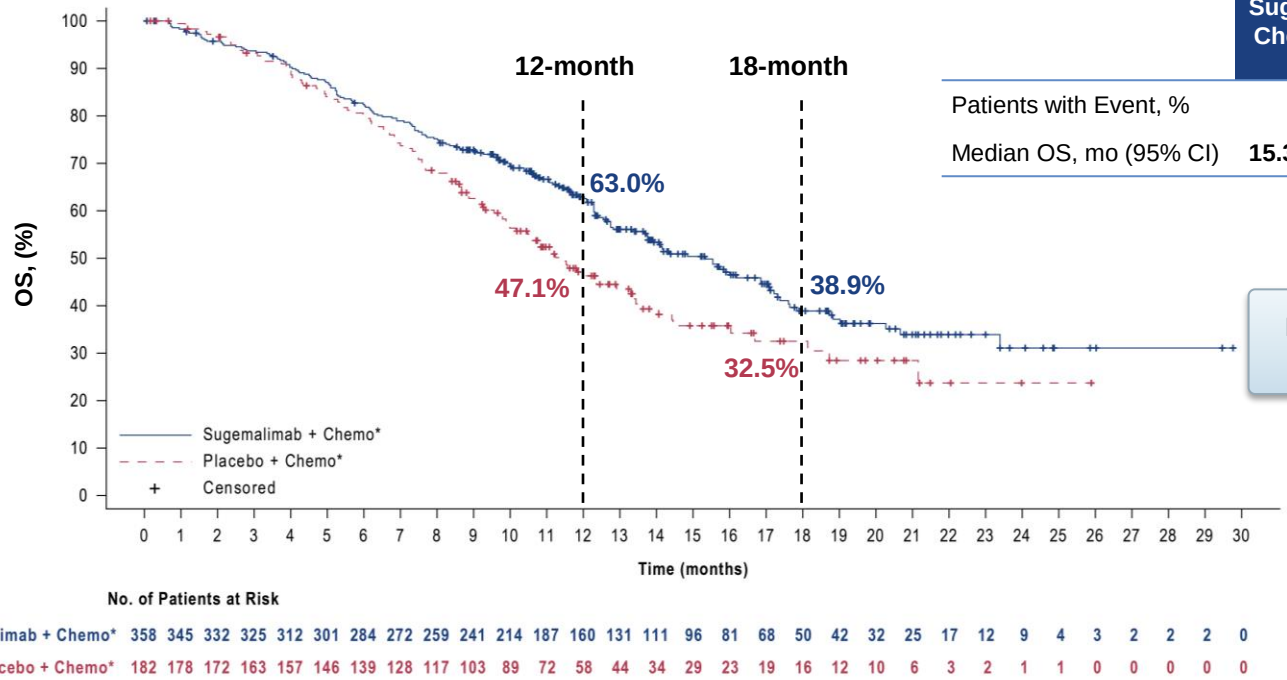


	Sugemalimab + Chemotherapy (N=358)	Placebo + Chemotherapy (N=182)
Patients with Event, %	74.0%	80.8%
Median PFS, mo (95% CI)	**6.2** (5.7, 6.9)	**5.4** (4.9, 5.8)

HR 0.67 (95% CI, 0.54-0.82)
***P* = 0.0002**

Data cutoff date: 07 Oct, 2022.
Summaries of progression-free survival (median, percentiles) are Kaplan-Meier estimates. Confidence interval for the median is calculated using the method by Brookmeyer and Crowley. HR is estimated using the stratified Cox proportional-hazards model. *P* value is based on stratified max-combo test. BICR:blinded independent central review; Chemo*: chemotherapy; CI: confidence interval; HR: hazard ratio; ITT: intent-to-treat; mo: month; PFS: progression-free survival.

Dual Primary Endpoints: OS in ITT Population



	Sugemalimab + Chemotherapy (N=358)	Placebo + Chemotherapy (N=182)
Patients with Event, %	49.2%	57.1%
Median OS, mo (95% CI)	**15.3** (13.3, 17.1)	**11.5** (9.9, 13.4)

HR 0.70 (95% CI, 0.55-0.90)
P [1] **= 0.0076**

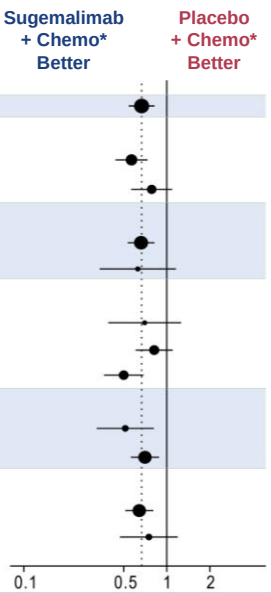
Data cutoff date: 07 Oct, 2022.
1. P value is based on stratified max-combo test. *P* value boundary for the interim analysis is 0.0148.
Summaries of overall survival (median, percentiles) are Kaplan-Meier estimates. Confidence interval for the median is calculated using the method by Brookmeyer and Crowley. HR is estimated using the stratified Cox proportional-hazards model.
Chemo*: chemotherapy; CI: confidence interval; HR: hazard ratio; ITT: intent-to-treat; mo: month; OS: overall survival.

Subgroup Analysis of PFS and OS in ITT Population

Consistent benefits of PFS and OS observed across almost all pre-specified subgroups, including all PD-L1 expression levels, baseline ECOG PS, metastasis, age, and gender.

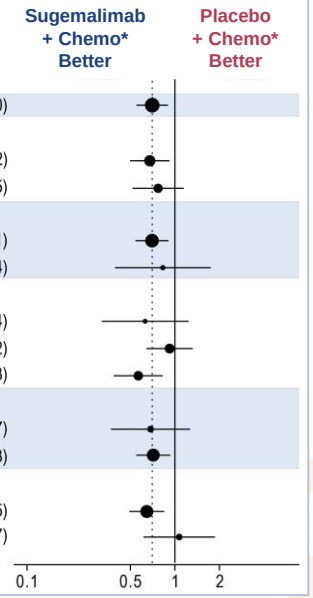
PFS by subgroup

Subgroup	Sugemalimab + Chemo* (N=358) Event/n	Placebo + Chemo* (N=182) Event/n	HR (95% CI)
All Patients	265/358	147/182	0.67 (0.54, 0.82)
Age Group (years)			
<65	166/216	91/106	0.57 (0.44, 0.73)
≥65	99/142	56/76	0.78 (0.56, 1.09)
Sex			
Male	236/314	131/158	0.66 (0.53, 0.82)
Female	29/44	16/24	0.63 (0.34, 1.16)
PD-L1 Score			
<1%	35/41	17/21	0.70 (0.39, 1.26)
≥1% and <10%	124/163	67/83	0.82 (0.61, 1.10)
≥10%	106/154	63/78	0.50 (0.36, 0.69)
Baseline ECOG			
0	51/75	31/39	0.51 (0.32, 0.81)
1	214/283	116/143	0.70 (0.56, 0.88)
Metastatic			
Yes	208/285	120/144	0.64 (0.51, 0.80)
No	57/73	27/38	0.75 (0.47, 1.19)



OS by subgroup

Subgroup	Sugemalimab + Chemo* (N=358) Event/n	Placebo + Chemo* (N=182) Event/n	HR (95% CI)
All Patients	176/358	104/182	0.70 (0.55, 0.90)
Age Group (years)			
<65	114/216	64/106	0.67 (0.50, 0.92)
≥65	62/142	40/76	0.77 (0.52, 1.15)
Sex			
Male	157/314	93/158	0.70 (0.54, 0.91)
Female	19/44	11/24	0.83 (0.39, 1.74)
PD-L1 Score			
<1%	23/41	14/21	0.63 (0.32, 1.24)
≥1% and <10%	88/163	45/83	0.92 (0.64, 1.32)
≥10%	65/154	45/78	0.57 (0.39, 0.83)
Baseline ECOG			
0	26/75	17/39	0.68 (0.37, 1.27)
1	150/283	87/143	0.71 (0.55, 0.93)
Metastatic			
Yes	136/285	86/144	0.65 (0.49, 0.85)
No	40/73	18/38	1.07 (0.61, 1.87)



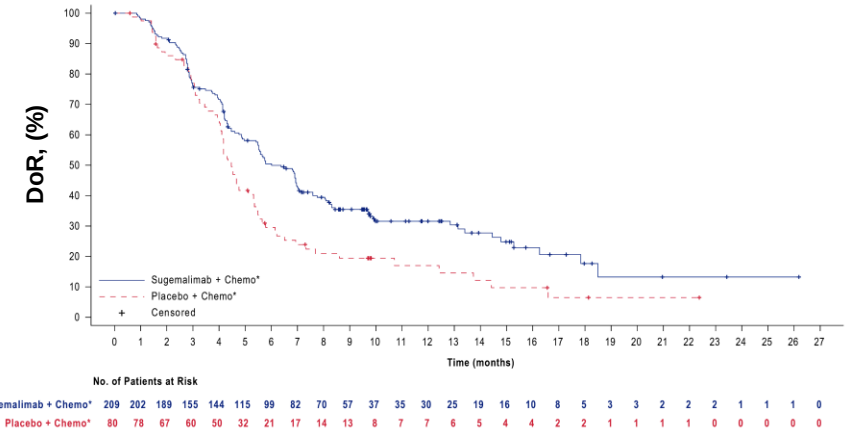
Data cutoff date: 07 Oct, 2022.

For subgroup analyses, HRs and the associated CIs are calculated using unstratified Cox Regression Model. Chemo*: chemotherapy; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; ITT: intent-to-treat; OS: overall survival; PD-L1: programmed death-ligand 1; PFS: progression-free survival.

Key Secondary Endpoints: BICR-assessed ORR and DoR

	Sugemalimab + Chemotherapy (N=348)	Placebo + Chemotherapy (N=177)
ORR[1] (CP+PR), n (%)	209 **(60.1%)**	80 **(45.2%)**
95% CI	(54.7%, 65.2%)	(37.7%, 52.8%)
Difference in ORR[2], 95% CI	14.9% (5.9%, 23.8%), *P* = 0.0011	
BOR[3], n (%)		
Complete response, n (%)	38 (10.9%)	9 (5.1%)
Partial response, n (%)	171 (49.1%)	71 (40.1%)
Stable disease, n (%)	89 (25.6%)	64 (36.2%)
Progression of disease, n (%)	16 (4.6%)	15 (8.5%)
Not evaluable	4 (1.1%)	1 (0.6%)
Not applicable [4]	30 (8.6%)	17 (9.6%)

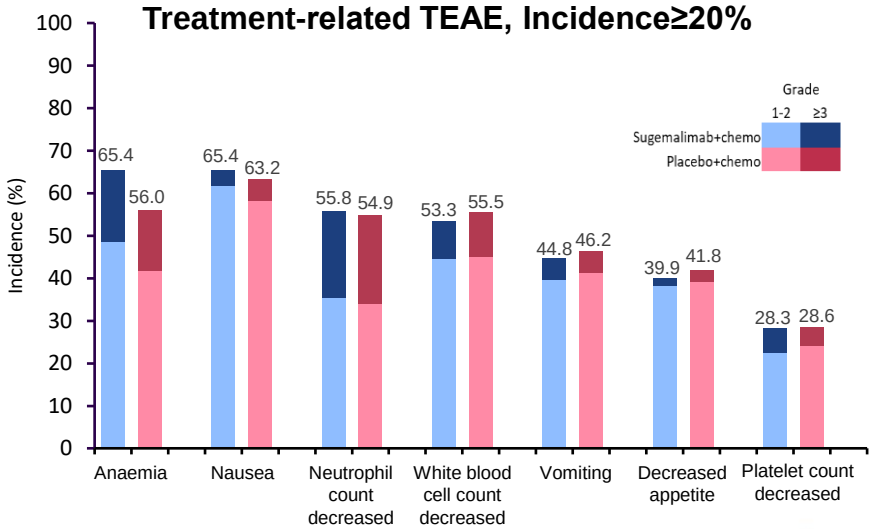
	Sugemalimab + Chemotherapy (N=209)	Placebo + Chemotherapy (N=80)
Median DoR, mo (95% CI)	**6.0** (5.5, 7.0)	**4.5** (4.1, 5.3)



1. 95% CI for ORR is calculated using Clopper-Pearson method. BICR-assessed ORR based on RECIST version 1.1. Tumor response was assessed in ITT population with measurable disease at baseline. 2. *P* value is calculated using the stratified by stratification factors (PD-L1, ECOG Performance Status and Distant Metastatic from IWRS) Cochran-Mantel-Haenszel Chi-Square test. 95% CI for difference in ORR is estimated using normal approximation of binomial distributions.3. Best overall response is defined as the best response during the period between the first dose and the first documented PD, death, or any new anti-cancer therapy, whichever occurs first. 4. Patients were classified as not applicable if no post-baseline response assessments were available. BICR:blinded independent central review; BOR: best overall response; Chemo*: chemotherapy; CI: confidence interval; CR: complete response; DoR: duration of response; mo: month; ORR: objective response rate; PR: partial response.

Overview of Adverse Events

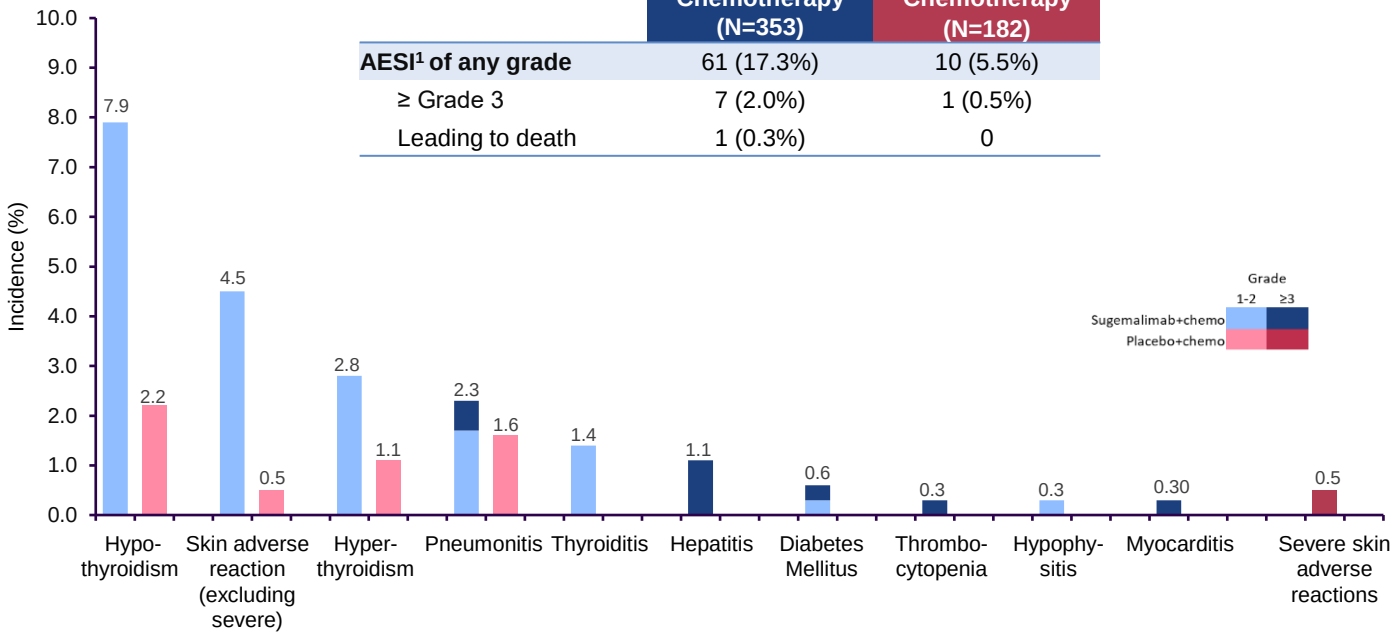
	Sugemalimab + Chemotherapy (N=353)	Placebo + Chemotherapy (N=182)
Any TEAE[1]	353 (100.0%)	181 (99.5%)
≥ Grade 3	238 (67.4%)	109 (59.9%)
Leading to any treatment discontinuation	47 (13.3%)	19 (10.4%)
Any treatment-related TEAE[2]	346 (98.0%)	178 (97.8%)
≥ Grade 3	181 (51.3%)	88 (48.4%)
Serious	76 (21.5%)	24 (13.2%)
Leading to death[3]	6 (1.7%)*	1 (0.5%)*



1. TEAE is defined as any AE that occurred or worsened on or after the start of study treatment. 2. Treatment-related adverse event is defined as any TEAE that is related to any treatment assessed by the investigators. 3. Any death due to disease progression is excluded from the AE summary. *Treatment-related TEAEs leading to death in the sugemalimab+chemo group were pneumonia (2 pts), pneumonitis, upper gastrointestinal haemorrhage, hepatic failure, and malnutrition (1 pt each); in the placebo+chemo group was pneumonia (1 pt). TEAEs were graded by NCI-CTCAE version 5.0. AE terms were coded using MedDRA version 25.1. Chemo: chemotherapy; TEAE: treatment-emergent adverse event.

Adverse Event of Special Interest

	Sugemalimab + Chemotherapy (N=353)	Placebo + Chemotherapy (N=182)
AESI[1] of any grade	61 (17.3%)	10 (5.5%)
≥ Grade 3	7 (2.0%)	1 (0.5%)
Leading to death	1 (0.3%)	0



1.The adverse events of special interest in this study are the sponsor-assessed immune-related AEs . The sponsor developed a query list of 24 categories of MedDRA PTs to identify irAEs based on the characteristics of immune-related adverse reactions of similar products, as well as the characteristics of immune-related adverse reactions in guidelines and literature.
Chemo: chemotherapy; irAE: Immune-related adverse event.

Conclusions

Sugemalimab plus chemotherapy (5-fluorouracil and cisplatin) provides a new first-line treatment option to patients with unresectable locally advanced, recurrent or metastatic ESCC

To our knowledge, the GEMSTONE-304 trial represents the first investigation of an anti-PD-L1 antibody plus chemotherapy showing significant improvement in both PFS and OS outcomes in the first-line setting for esophageal cancer

- **Sugemalimab in combination with chemotherapy demonstrated statistically significant and clinically meaningful prolongation in PFS & OS and improvement of ORR vs. chemotherapy**
  - BICR-assessed PFS: median 6.2 vs. 5.4 months, HR 0.67 (95% CI, 0.54-0.82), *P*=0.0002
  - OS: median 15.3 vs. 11.5 months, HR 0.70 (95% CI, 0.55-0.90), *P*=0.0076
  - Consistent benefits of PFS and OS observed across almost all pre-specified subgroups, including different PD-L1 expression levels, baseline ECOG PS, metastasis, age, and gender
  - BICR-assessed ORR: 60.1% vs. 45.2%
  - BICR-assessed DoR: median 6.0 vs. 4.5 months

- **Sugemalimab plus chemotherapy showed a manageable safety profile, with no new safety signals detected**

BICR:blinded independent central review; DoR: duration of response; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ESCC: Esophageal Squamous Cell Cancer; HR: hazard ratio; ORR: objective response rate; OS: overall survival; PD-L1: programmed death-ligand 1;PFS: progression-free survival;

Acknowledgements

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